PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for the ROBUST (Registry Of type B aortic dissection with the Utility of STent graft) study: an ambispective, multi-center, open cohort study
AUTHORS	Rong, Dan; Ge, Yangyang; Xue, Yan; Liu, Feng; Lu, Kai; Liu, Peng; Zhang, Lei; Ge, Xiaohu; Miu, Jianhang; Zhong, Linkun; Fan, Weidong; Zhang, Hongpeng; Jia, Xin; Ma, Xiaohui; Xiong, Jiang; Liu, Xiaoping; Guo, Wei

VERSION 1 – REVIEW

REVIEWER	HIROO TAKAYAMA COLUMBIA UNIVERSITY, USA
REVIEW RETURNED	20-Sep-2017

GENERAL COMMENTS	This is a description of a protocol that is to investigate a clinical utility of TEVAR therapy for type B aortic dissection. As the authors eluded, it is an important and timely topic. The intent of the study is relevant and the results could be quite influential. The authors ambitiously plan to enroll close to 200 patients with long-term follow-up. The methodology would benefit from further revision. Please see my comments below: 1. Most important, the primary end point is unclear. In the Objective, it is described as 'to identify predisposing risk factors and prognostic factors for adverse events, in particular, adverse false lumen thrombosis after TEVAR in a real-world setting'. I just don't understand what the actual measurable variable is here. I recommend further clarifying the primary end point. 2. In the same context, the sample size calculation is compromised due to this ambiguous definition of the primary end point. Again, what is the variable and what is the expected change, which is the critical estimation in sample size calculation. 3. What does the author mean by 'real-world setting'? There are a number of published single center series, and in the current format, this study will be similar to them. What is the novelty? 4. More useful variables could be included in the database. The following are just examples of such variables: symptom, interval from the onset to the intervention, use of CSF drainage, information on left vertebral artery, aortic reintervention. Thank you very much for allowing me to review this proposal.

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REVIEWER	Bektas Battaloglu Inonu University Faculty of Medicine Malatya-TURKEY
REVIEW RETURNED	26-Sep-2017

GENERAL COMMENTS	Even though, TEVAR is applied in type B aortic dissection for a long period, it is still associated with high complication rates and mortality. In addition, long-term benefits of this method are limited.To identify patients who best benefit from TEVAR with low risk deserves appreciation. In this context it is a valuable study becouse of the registry aimed to identify criterias for determining the patients will most benefit from TEVAR. It also makes it more valuable, as it is comprehensive and long-term study provided to keep the patients on tract.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: HIROO TAKAYAMA
Institution and Country: COLUMBIA UNIVERSITY, USA
Please state any competing interests or state 'None declared': NONE DECLARED

Please leave your comments for the authors below
This is a description of a protocol that is to investigate a clinical utility of TEVAR therapy for type B aortic dissection. As the authors eluded, it is an important and timely topic. The intent of the study is relevant and the results could be quite influential. The authors ambitiously plan to enroll close to 200 patients with long-term follow-up. The methodology would benefit from further revision. Please see my comments below:

1. Most important, the primary end point is unclear. In the Objective, it is described as 'to identify predisposing risk factors and prognostic factors for adverse events, in particular, adverse false lumen thrombosis after TEVAR in a real-world setting'. I just don't understand what the actual measurable variable is here. I recommend further clarifying the primary end point.

Response:
Thanks for your suggestion. Primary end point in present study is dissection aneurysm formation (defined as > 5mm increase in maximum aortic diameter during a follow-up time point compared with the measurement at preoperative examination, or a maximum aortic diameter □ 55mm). Distal dissection aneurysm formation is the main conplication after TEVAR, 5-year incedence is about 63% according to previous studies [1]. Our study focuses mainly on revealing prognostic factors for this end pont. We will specify the end point in the objective section of manuscript.
Corrections:
Line 104-111:
The primary objective of the registry is to identify predisposing risk factors and prognostic factors for adverse events in a real-world setting. Primary end point in present study is dissection aneurysm formation (defined as □ 5mm increase in maximum aortic diameter during a follow-up time point compared with the measurement at preoperative examination, or a maximum aortic diameter □ 55mm). Secondary endpoint is a composite endpoint including aortic-related death, endoleaks, retrograde type A aortic dissection, stent-graft-related new entry, aortic rupture and impending rupture.

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2. In the same context, the sample size calculation is compromised due to this ambiguous definition of the primary end point. Again, what is the variable and what is the expected change, which is the critical estimation in sample size calculation.

Response:
Previous studies pertaining to the effect estimation of a certain risk factor for the post-TEVAR aortic remodeling are limited. According to the results of our two previously published studies focusing on the association of the preoperative thoracic false lumen branches and the thoracic aortic enlargement after TEVAR, the point estimation of coefficient of the preoperative thoracic false lumen branches is 0.37 (95% CI, 0.18-0.57) for the association with the risk of thoracic aortic enlargement distal to stent-graft, and 1.17 (95%CI, 0.20-2.14) for the association with the risk of thoracic aortic enlargement along the stent-graft [2, 3]. Furthermore, the R-Squared of the preoperative thoracic false lumen branches with other covariates ranges from 0.254 to 0.301. Additionally, our previous study and the STABLE trial reported that the incidence of thoracic aortic enlargement at 24 months after surgery ranges from 24% to 26%. Based on these data, we conservatively used effect size of 0.18, R-Squared of 0.35 and anticipated event rate of 20% to calculate the sample size. A minimum sample size of 93 patients will be included to achieve 80% power at a 0.05 significance level.
Corrections:
Line 30-33:
All patients undergoing TEVAR from January 1, 2008 to July 1, 2027 at participating centres will be invited to join the study. It is conservatively estimated that over 2000 patients will join the study.
Line 179-206:
Previous studies pertaining to the effect estimation of a certain risk factor for the post-TEVAR aortic remodeling are limited. According to the results of our two previously published studies focusing on the association of the preoperative thoracic false lumen branches and the thoracic aortic enlargement after TEVAR, the point estimation of coefficient of the preoperative thoracic false lumen branches is 0.37 (95% CI, 0.18-0.57) for the association with the risk of thoracic aortic enlargement distal to stent-graft, and 1.17 (95% CI, 0.20-2.14) for the association with the risk of thoracic aortic enlargement along the stent-graft [26, 27]. Furthermore, the R-Squared of the preoperative thoracic false lumen branches with other covariates ranges from 0.254 to 0.301. Additionally, our previous study and the STABLE trial reported that the incidence of thoracic aortic enlargement at 24 months after surgery ranges from 24% to 26%. Based on these data, we conservatively used effect size of 0.18, R-Squared of 0.35 and anticipated event rate of 20% to calculate the sample size. A minimum sample size of 93 patients will be included to achieve 80% power at a 0.05 significance level. However, the estimated sample size should be interpreted carefully, since the adopted data are derived from the study regarding the thoracic aortic remodeling rather than from the database focusing on aortic remodeling along both thoracic and abdominal aorta.From 2008 to 2017, more than 500 patients with type B aortic dissection have received endovascular repair in our hospital. More than 50 patients in our hospital and 30 patients in other 4 participating centres receive TEVAR every year. We will recruit patients consecutively from 2017 to 2027. A total number of 2000 patients are conservatively estimated to join the cohort, which is well exceed 93.

3. What does the author mean by ‘real-world setting’? There are a number of published single center series, and in the current format, this study will be similar to them. What is the novelty?

Response:
Unlike RCTs, real-world evidence studies use observational data. There are still controversies about when to receive TEVAR procedures for patients with uncomplicated type B aortic dissection. Different hospitals may use diferent treatment for the same patient. To creat deeper insights into indications of TEVAR and to identify which subgroup of patients would benefit the most from TEVAR, our study process will not influence clinical practice. In our study, real-world setting means noninfluence on clinical practice, wider inclusion criteria, less exclusion criteria, and long-term follow up.

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And speaking of novelty, first of all, this is the first registry study of TEVAR in patients with type B aortic dissection in Chinese population. Chinese population have a higher incidence and a younger average age of aortic dissection than western population, while there is no registry study to identify morphologic prognostic factors for major adverse events (including death and distal dissection aneurysm formation). And this is the first registry study mainly focusing on imaging features that affect the outcomes of patients after TEVAR, we used more than 100 imaging features as variables to address the objectives.

4. More useful variables could be included in the database. The following are just examples of such variables: symptom, interval from the onset to the intervention, use of CSF drainage, information on left vertebral artery, aortic reintervention.

Response:
Thanks for your suggestion. As you mentioned above, we will include chest or back pain, unconsciousness, breathlessness, and hypotension as variables concerning symptoms, we will also include use of CSF drainage and patency of left vertebral artery as variables to identify the effects on spinal cord ischemia. As regards aortic reintervention, we have already included this variable in our study.
Corrections:
Line 157-177:
1. Demographics and disease history: Age, gender, height, weight, tobacco consumption, chest or back pain, unconsciousness, breathlessness, hypotension, drinking habits, diabetes mellitus, hypertension, dyslipidaemia, ischemic stroke, coronary artery disease, carotid stenosis, and chronic obstructive pulmonary disease.
2. Surgical information: Operation indication, American Society of Anesthesiologists (ASA) physical status class, brand of stent-graft, number of stent-grafts, status of left subclavian artery (covered, uncoverd, or reconstructed), status of left common carotid artery (covered, uncoverd, or reconstructed), blood loss, contrast medium volume, type I endoleak during procedure, use of cerebrospinal fluid drainage, and conversion to open surgery.
3. Preoperative imaging features: Periaortic hematoma, impending rupture, pleural effusion, dissection length, primary tear location, branch arteries involvement, distal outflow track status, false lumen thrombosis status, diameter of aorta, true lumen, and false lumen at different levels, volume of aorta, true lumen, and false lumen.
4. Outcomes: Periaortic hematoma, impending rupture, pleural effusion, proximal endoleak, stent-graft induced new entry, retrograde dissection, new reentry tear in lower thoracic aorta, number of intimal tears, patency of left subclavian artery, patency of left vertebral artery, branch arteries involvement, false lumen thrombosis status of stent-graft-covered segment, diameter of aorta, true lumen, and false lumen at different levels, volume of aorta, true lumen, and false lumen, ischemic stroke, myocardial infarction, arterial embolism in lower limbs, paraplegia, and death.

Thank you very much for allowing me to review this proposal.

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Reviewer: 2
Reviewer Name: Bektas Battaloglu
Institution and Country: Inonu University Faculty of Medicine, Malatya-TURKEY
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

Comment: Even though, TEVAR is applied in type B aortic dissection for a long period, it is still associated with high complication rates and mortality. In addition, long-term benefits of this method are limited. To identify patients who best benefit from TEVAR with low risk deserves appreciation. In this context it is a valuable study becouse of the registry aimed to identify criterias for determining the patients will most benefit from TEVAR. It also makes it more valuable, as it is comprehensive and long-term study provided to keep the patients on tract.

Response:
Thanks for your comments. TEVAR reduced perioperative mortality compared with open surgery. However, there are still controversies about which subgroup of patients benefit most from TEVAR, when to perform TEVAR especially for patients with uncomplicated type B aortic dissection, and which subgroup of patients will develop into dissection aneurysm. Our study aims to answer these questions. Apparently, as you said, it is very hard to keep in touch with patients in a long-term follou up. We will try some new solution to this problem, for example, a cloud platform. Patients can upload their CTA images, and we will contact them online. Even so, lost to follow up might become a limitation of our study.
References:
[1]. Fattori, R., et al., Survival After Endovascular Therapy in Patients With Type B Aortic Dissection. JACC: Cardiovascular Interventions, 2013. 6(8): p. 876 - 882.
[2]. Ge, Y.Y., et al., Preoperative thoracic false lumen branches relate to aortic remodeling after thoracic endovascular aortic repair for DeBakey IIIb aortic dissection. J Vasc Surg, 2017. 65(3): p. 659-668.e2.
[3]. Liu, F., et al., Preoperative thoracic false lumen branches are predictors of aortic enlargement after stent grafting for DeBakey IIIb aortic dissection. J Thorac Cardiovasc Surg, 2017.

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